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THE PRESENT STATUS OF PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*

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BEFORE the discovery of penicillin there was no specific form of treatment for subacute bacterial endocarditis. Except in the unusual, mild forms of the disease,[1, 2] spontaneous recovery was infrequent and occurred in but 3 to 4% of cases.[3] The prognosis was but little altered by treatment with the sulfonamide group of chemotherapeutic agents. While early results with penicillin therapy were none too encouraging,[4] it soon became obvious that a higher percentage of apparent cures might be expected than from previous methods of treatment. This stimulated a more intensive study by physicians on this continent and in Great Britain and, on the basis of results achieved, it is now generally agreed that treatment of subacute bacterial endocarditis with penicillin results in arrest of the infection in a large percentage of cases.[5 to 13] Though proved the most effective agent yet employed, penicillin still presents many problems of treatment. Foremost among these are: the amount of the antibiotic which constitutes adequate dosage; the duration of treatment; and the method of administration. It is in an attempt to elucidate these as well as some other related problems that the present series of 15 cases is presented.

The cases in this series were consecutive, and the sole basis of selection was that the patient suffered from subacute bacterial endocarditis. In all 15 cases the diagnosis was established by the presence of fever, endocardial disease, and repeated positive blood cultures. In the majority, there were one or more of the other usual manifestations of the disease including petechiæ, splenomegaly and embolism. Penicillin was administered by either the intravenous or intramuscular route, continuous intramuscular injection being the method usually adopted. This latter method was facilitated by the use of a special apparatus designed to deliver 250 to 500 c.c. of penicillin in normal saline in a twelve hour period. In certain cases a combination of the continuous intramuscular and intravenous routes was necessitated by pain or infection at the site of the continuous intramuscular injection.

Prior to the institution of therapy, the sensitivity of the offending micro-organism was determined by *in vitro* tests. During the course of treatment, blood cultures were obtained at least twice weekly and, in all but early cases, penicillinase was added to the media to avoid fictitious negative results. Additionally, in those cases wherein blood cultures continued to reveal the presence of the organism during treatment, further *in vitro* sensitivity tests were made. The level of penicillin in the blood serum was estimated generally twice weekly, when the method for assessing such became available. The amount of penicillin given varied between 100,000 and 1,000,000 units daily, the amount given to certain early cases being determined largely by the availability of the antibiotic. The usual period of treatment was twenty-eight days. In some cases, a

TABLE I.

RESULTS OF PENICILLIN TREATMENT IN 15 CASES OF SUBACUTE BACTERIAL ENDOCARDITIS*

Result	*No. of cases*
Clinical arrest	5
Probable clinical arrest—death due to sequelæ of primary disease	5
Treatment failure	5

*In two additional cases it is as yet too early to determine the result of treatment.

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TABLE II.

TREATMENT OF 15 CASES OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN

Pt. Age Sex	Heart disease	Probable duration S.B.E.	Bacteria		Penicillin							Complications	Result of treatment
								Serum concentration					
			Type	In vitro sensitivity	Duration of treatment	Dosage	Route	Variation	Average	In terms of in vitro sensitivity	Tests		
					days	units		u/c.c.	u/c.c.		No.		
B.E. F-67	H.B.P. M. Ins.	6 wk.	Strep. virid.	0.125	28	700,000	C.I.M.	1.0-3.2	1.7	x13	8	Cerebral and pulmonary emboli.	Clinical arrest—17 months.
J.Mc. M-55	Rheum. A.Ins.	3 wk.	Strep. non-h.	0.125	32	400,000	C.I.M.	0.24-0.8	0.53	x4	9	Pulmonary embolus, 10th day of treatment.	Clinical arrest—15 months.
M.C. F-37	Rheum. M.Ins.	5 wk.	Strep. virid.	0.03	33	120,000	C.I.M. I.V.	0.06-0.03 0.00-0.03	0.12	x4	2	None.	Clinical arrest—13 months.
C.W. M-47	Rheum. A.Ins.	3 mo.	Strep. virid.	0.03	28 (6 22)	400,000 800,000	I.V. I.V.	0.06- 0.15		x5	1 1	None.	Clinical arrest—14 months.
R.A. F-15	Patent ductus	4 mo.	Strep. virid.	0.015	28	200,000	C.I.M.	0.05-0.75	0.27	x18	8	Pulmonary embolus, 21st day of treatment.	Clinical arrest—8 months.
J.K. F-20	Patent ductus Arter.	6 mo.	Strep. virid.	0.015	29	150,000	C.I.M.	0.5-1.6	1.26	x80	7	Abscess at injection site; acute nephritis; congestive failure.	Died 24th day after cessation of therapy, of nephritis and congestive failure. Probable clinical arrest.
M.W. F-53	Rheum. M.Ins.	6 wk.	Strep. virid.	not estimated	38	120,000 q. 4 h.	I.M. I.V.	not estimated				Femoral embolus 4th day, and atelectasis 8th day of treatment.	Died 28th day after treatment of atelectasis and failure. Post mortem examination: endocarditis healed. Probable clinical arrest.
S.A. F-18	Rheum. M.Ins.	6 mo.	Strep. virid.	0.024	19	200,000	C.I.M.	0.24-0.8	0.46	x19	3	Cerebral embolus, 19th day of treatment.	Died of cerebral embolus while on treatment. Probable clinical arrest.
J.H. M-31	Rheum. M.Ins.	8 mo.	Strep. virid.	0.004	26	120,000	C.I.M.	0.1			1	Cerebral embolus, 23rd day of treatment. Femoral embolus, 2nd day after cessation of treatment. Cerebral embolus, 6th day after cessation of treatment.	Died 6 days after treatment of cerebral embolus. Probable clinical arrest.
J.C. M-41	Luetic aortitis	10 wk.	Strep. virid.	0.05	32 (7 25)	120,000 240,000	C.I.M. C.I.M.	0.19 0.38-2.0	0.95	x19	5	Congestive failure.	Died of congestive failure. Blood cultures negative and patient afebrile on cessation of treatment. Post mortem examination: bacterial endocarditis healing. Probable clinical arrest.
J.C. M-37	Congen. bicusp. aorta	6 mo.	Strep. virid.	0.004	6	100,000	C.I.M.	not estimated				Congestive failure. Cerebral hæmorrhage, 6th day of treatment.	Died of congestive failure and cerebral hæmorrhage while on treatment.
E.E. F-42	Rheum. A.Ins.	6 mo.	Strep. non-h.	not estimated	28	120,000	C.I.V.	not estimated	?			None.	Died. Cultures positive on treatment.
L.S. F-33	Rheum. M.Ins.	2 mo.	Strep. virid.	0.5-4.0	40	120,000	C.I.M.	0.05-0.1		x.1 to x.4	3	None.	Died. Cultures positive on treatment.
R.W. M-24	Congen. heart	5 wk.	Strep. virid.	0.063	18	120,000	C.I.M. I.V.	0.05			1	None.	8 of 10 cultures positive.
				0.063	22	240,000	C.I.M.	0.11-0.14			2	None.	6 of 8 cultures positive.
				0.063	33	500,000	C.I.M.	0.13-0.8	0.49		8	None.	6 of 18 cultures positive.
				0.063	28	1,000,000	C.I.M.	0.6-2.4	1.0	x16	9	None.	Cultures negative but immediately became positive on cessation of treatment.
S.M. M-49	Rheum. M.S.	12 mo.	Strep. virid.	0.004-0.03	32	100,000	C.I.M.	0.15-0.24	0.20	x50-x8	4	Congestive failure. Pulmonary embolus, 2nd day of treatment.	Died. Blood cultures negative, then positive while on treatment.

longer period of treatment was employed when progress appeared unsatisfactory.

The term "clinical arrest" is used to designate the result of treatment in those patients who were rendered free and remained free of evidence of infection following penicillin therapy. The results are synopsized in Table I and Table II. Five of the 15 cases of subacute bacterial endocarditis may be recorded as clinically arrested. In all 5, blood cultures promptly became negative and remained so, and the patient was rendered free of the constitutional manifestations of the disease. These 5 patients have remained free of signs of infection for 17, 15, 13, 14 and 8 months respectively.

Five further cases were probably clinically arrested. In three of these the infection appeared to be clinically arrested but death due to sequelæ of the primary disease occurred. One of these patients succumbed to congestive failure and collapse of the lung twenty-nine days after cessation of treatment. An examination post mortem revealed that the endocarditis caused by the *Streptococcus viridans* was healed. Another succumbed to nephritis and congestive failure twenty-eight days after termination of therapy. Death in the third was also due to congestive failure. At examination post mortem in this case, culture of one of the vegetations was sterile and the microscopic appearance of the vegetations was in keeping with a healing process. In all three, serial blood cultures were negative during and following treatment. Two patients died of cerebral embolus, one on the nineteenth day of treatment and the other six days after treatment was discontinued. In both, blood cultures became and remained sterile on institution of therapy.

Five cases were outright treatment failures. In one, the cause of failure was attributed to a highly resistant micro-organism: an *in vitro* sensitivity test revealed that 0.5 units of penicillin per c.c. of culture media was required to inhibit growth of the organism. The patient received 120,000 units of penicillin daily for forty days. Cultures remained positive and serial *in vitro* sensitivity tests showed that under treatment the organism became increasingly resistant to the antibiotic. Whereas the initial sensitivity was 0.5 units of penicillin per c.c., this decreased to 4.0 units of penicillin per c.c. at the end of treatment. In the second case, failure may have been attributable to the same cause. This was the first case treated and facilities to determine the sensitivity of the strain were not available. Blood cultures remained positive throughout the twenty-eight day course of treatment. The reason for failure in the remaining three cases is not clear. In one of these, the micro-organism revealed an initial *in vitro* sensitivity of 0.004 units of penicillin per c.c. and a final sensitivity of 0.03 units. This patient received 100,000 units of penicillin daily for thirty-two days. An average penicillin blood concentration of 0.20 units per c.c. was maintained which, based on *in vitro* sensitivity, theoretically was more than adequate. Blood cultures in this case became sterile initially but before termination of treatment again yielded the micro-organism. In the fourth case, the micro-organism on *in vitro* test revealed a sensitivity of 0.004 units of penicillin per c.c. The patient received 100,000 units of penicillin daily; blood cultures remained positive and death, as a result of cerebral accident, occurred on the sixth day of treatment. The serum level of penicillin in this case was not estimated. In the fifth instance of failure, the patient was under treatment for 101 days and in this period received 51,940,000 units of penicillin. For periods of 18, 22, and 33 days, the patient received 120,000, 240,000 and 500,000 units of penicillin daily, respectively; then, after an interval of 38 days, received 1,000,000 units daily for 28 days. *In vitro* sensitivity tests revealed a constant sensitivity of 0.063 units. Only on doses of 1,000,000 units daily, which maintained an average serum concentration of 1.0 unit, did the blood cultures become negative, but on discontinuance of therapy they promptly became positive again. In considering the reasons for this failure, both a refractory strain of *Strep. viridans* and an insufficient period of treatment must be taken into account.

DISCUSSION

It is a general principle that, to achieve a good result with an antibiotic, not only must contact be established and maintained between the micro-organism and the antibiotic, but also the concentration of the bacteriostatic agent must be maintained at effective levels for a sufficient time interval.[14] Subacute bacterial endocarditis affords a unique and difficult problem in this respect because of the relative

avascularity of the valve leaflets and vegetations and the fact that colonies of bacteria are located not only on the surface of the vegetations but also in the depths of the endocardial lesions. From a consideration of the character of the endocardial lesions at different stages of the disease, it would appear that long duration of the disease would adversely affect the response to treatment. As the bacteria are more deeply located in lesions of long standing, it would seem reasonable to assume that in such cases a more prolonged period of treatment may be required. While the number of cases under discussion is too small to be statistically significant or upon which to base a final conclusion, it is of interest that the average known duration of the disease in the 5 clinically arrested cases was 8 weeks, as compared to 23 weeks for the cases wherein treatment failed to influence the course of the disease. These findings tend to suggest that a longer and possibly more intensive course of treatment may be indicated for cases of long standing.

Adequate dosage is difficult to define. While there continues to be considerable diversity of opinion, both with respect to the optimal daily dosage and duration of treatment, our results are in accord with those[5, 9, 10, 12, 13] who favour a daily dose of 200,000 to 500,000 units of penicillin for periods of three weeks or more. It is known that amounts of 100,000 to 150,000 units occasionally do arrest the infection, but it would seem generally agreed that in the average case of subacute bacterial endocarditis dosage less than 200,000 units daily is likely to prove inadequate. While clinical cure is the only proof that sufficient penicillin has been administered, the clinical course of the patient while undergoing treatment does afford evidence as to whether or not the amount of penicillin employed is likely to be sufficient. If blood cultures promptly become sterile and the patient becomes afebrile within a few days of institution of therapy, there would seem to be evidence that the amount of drug being administered may be considered adequate. A daily dose of 200,000 units of penicillin for a period of twenty-eight days is recommended for the treatment of the majority of cases of subacute bacterial endocarditis. The amount of the antibiotic should be increased promptly, however, if the clinical response to treatment during the first week is unsatisfactory. In such cases, if blood cultures remain positive and/or the patient remains febrile, an increase in the daily dose of penicillin to 500,000 units is recommended. There would seem little justification for any further increase in the daily dosage. In connection with the duration of treatment, because the relative avascularity of the bacterial vegetations must result in delayed healing, a minimum period of 28 days is recommended. It is emphasized, however, that, while this period of 28 days' treatment usually is adequate, a longer period of treatment may be necessary if the disease is of long duration or if the clinical response is unsatisfactory.

With reference to clinical response to treatment it must be added that in certain cases, although blood cultures promptly become sterile and remain negative and the patient becomes afebrile, fever may recur later; or, with the institution of treatment, there may be a fall in temperature but the patient does not become afebrile. In such cases, one must investigate other possible causes of continued or recurrent fever, such as: reaction to the penicillin, an inflammatory reaction at the site of intramuscular injection, infarction of the lung or other organ, or peripheral arterial embolism. In one of our successfully treated cases, unexplained fever persisted for twelve days after cessation of treatment. As continued fever in patients with persistently negative blood cultures may be attributable to a complication of the disease or of the penicillin treatment, it is not necessarily an indication of inadequate therapy or for increasing the dose of the antibiotic.

In vitro sensitivity tests are a rough but not infallible guide to the amount of penicillin likely to be required in any particular case. A good result is more apt to be achieved if the micro-organism is moderately or highly sensitive on *in vitro* tests, and a successful outcome is improbable if the micro-organism has a low sensitivity. On the evidence available, it would seem desirable to employ a daily dose of penicillin sufficient to yield a serum concentration of at least five times that required to inhibit growth *in vitro*.[14] In an occasional patient, the micro-organism may be of moderate or even high sensitivity and the serum concentration apparently more than adequate but the patient fails to respond to treatment. In such cases, the cause of treatment failure in problematical.

Good results have been obtained by administering penicillin both intravenously and intramuscularly. The continuous intravenous drip, while it is technically the most difficult method, usually causes the patient the least distress.[5] With respect to intramuscular injections, it has recently been suggested[12] that there is little to choose in terms of results achieved between the constant intramuscular drip and intramuscular injections at intervals of three hours. It remains problematical whether a constantly maintained effective level of penicillin in the blood stream achieves deeper penetration into the vegetations than the intermittent though higher serum levels obtained by injections at intervals of three hours or more. The method that achieves maximum penetration no doubt is the method of choice. The decision in relation to this problem must rest on the results obtained in large series of cases. At the present time it would appear justifiable to employ either method in the treatment of cases of subacute bacterial endocarditis.

A factor which played a predominant rôle with regard to the final result of treatment in this series of cases was sequelæ of the primary disease. Five patients, in which there was reasonable clinical evidence that the bacterial infection was arrested, succumbed to sequelæ of the bacterial endocarditis or the underlying heart disease. As might be expected, the duration of bacterial endocarditis was considerably longer in these cases than in the successfully treated group. The influence of the natural course of the disease upon results of treatment therefore is stressed, and it is emphasized that, by reason of usual complications of this disease, there will always be a considerable mortality. In view of these frequent complications, the difficulties encountered in treating patients with penicillin, the need for the usual symptomatic treatment of the patient, as well as the advisability of having *in vitro* sensitivity tests made, it is suggested that institutional treatment of all patients is conducive to the best results.

SUMMARY AND TENTATIVE RECOMMENDATIONS FOR TREATMENT

1. In the majority of cases of subacute bacterial endocarditis, a daily dosage of 200,000 units of penicillin for a period of 28 days is considered an adequate course of treatment.

2. If the clinical response to treatment in the first week is unsatisfactory, a prompt increase in dosage to 500,000 units daily is considered advisable.

3. If the disease has been of more than average duration before institution of treatment, it may be advisable to prolong the course of treatment.

4. Both the continuous intramuscular drip and intramuscular injections at intervals of three hours are considered to be satisfactory methods of administering penicillin.

5. On the basis of results obtained in this series of cases, it is considered that clinical arrest if not permanent cure of the disease may be anticipated in at least 50% of cases.

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PETHIDINE AS A DRUG OF ADDICTION.—Dr. A. Harbour (London, S.W.1) writes: It may not be generally known that pethidine may cause addiction in as serious a degree as the more common drugs associated with this condition. A case seen by me lately brings this out clearly. The patient, a man of colour, was under my care for some 36 hours while being held by the police on a charge unconnected with his addiction. He had been a heroin addict but had been cured by the substitution of pethidine and no longer took the former drug except on rare occasions. On the other hand he needed three injections a day of 400 mgm. of pethidine to keep under control. Deprived even for a very short time of his drug he behaved in the normal way of an addict deprived of his "shot". Two points arise from this case. First, that physicians who relieve an addiction to one of the common drugs by substituting pethidine run the risk of a mere alteration of the addiction and a continuance of the misery and vice that goes with such a condition; and secondly, that the present position relating to the supply of pethidine whereby an addict can have a prescription repeated *ad lib.* or can obtain the drug without a prescription on signing the poison book at a chemist is unsatisfactory.—*Brit. M. J.*, September 21, 1946.